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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 16

Application Number: 09/526,298
Filing Date: March 15, 2000
Appellant(s): EVANS ET AL.

Mailed 5/14/02

Stephen Reiter
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 3/26/02 (certificate of mailing 3/21/02).

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is incorrect. A correct statement of the status of the claims is as follows:

This appeal involves claims 14-19 and 35-48.

Claims 49-53 have been canceled.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is incorrect.

The amendment after final rejection filed on 12/6/01 has been entered (it is noted that box 7 on the advisory action mailed 1/2/02 was not checked, but box (b) of 7 is checked indicating that the amendment will be entered).

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The appellant's statement in the brief that certain claims do not stand or fall together is not agreed with because the same issues of non-enablement are shared by all appealed claims. Applicants brief does not argue claims separately and further provides no explanation or reasons why the claims stand or fall together.

(8) Claims Appealed

A substantially correct copy of appealed claim14-19 and 35-48 appears on page 1-6 of the Appendix to the appellant's brief. The minor errors are as follows: The appendix includes copies of canceled claims 49-53 which are not part of the instant appeal.

(9) Prior Art of Record

Verma et al., "Gene Therapy- Promises, Problems and Prospects" Nature, Vol. 389:239-242, 1997.

Crystal, R., "Transfer of Genes to Humans: Early Lessons and Obstacles to Success" Science, Vol. 270:404-410.

Orkin et al., "Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy" 12/07/95.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 14-19 and 35-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a methods drawn to the induction or repression of a specific gene by a member of the steroid/thyroid superfamily of receptors which associates with at least the dimerization domain of ultraspiracle

receptor, in the presence of ligand for said member, where the expression of said gene is maintained under the control of a hormone response element to which said member binds where the method comprises exposing the expression system to at least the dimerization domain of an ultraspiracle receptor where the method is *in vitro* or in cells in culture, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims drawn to nucleic acid based therapy.

Claims 14-19 and 35-48 are drawn to nucleic acid based therapies.

The instant claims are drawn to nucleic acid therapy and involve methods of introducing and expressing exogenous genes and nucleic acid sequences in specific cells in a whole animal. For example, the claims require the integration of a gene coding for an ultraspiracle receptor and/or the introduction of a construct containing the hormone response sequence where said construct would further comprise a desired exogenous gene to be regulated by the ultraspiracle receptor (see pages 10, 21, and 22 of the instant specification, for example).

The art of gene therapy is an unpredictable art that requires much guidance. The instant specification provide guidance for the instant methods in cells in culture but does not provide guidance or example that would show by correlation the instant methods as they are drawn to nucleic acid based therapies. For example, the instant specification fails to teach one of skill in the art how to integrate the gene construct for the exogenous ultraspiracle receptor to specific desired cells such that expression would be at a level adequate for inducing the expression of a gene under the appropriate hormone reponse

element. The targeting of specific cells would be required, for example in cases where, as applicant contemplates and claims, a method of selectively killing cells and for directing expression of a desired gene in a specific cell type or tissue type. The instant specification fails to provide adequate guidance for one of skill in the art to create a "pre-existing system in an animal" and apply the instant methods. The establishment of such a system requires the introduction of an exogenous nucleic acid construct into cells of an animal and also to provide at least the dimerization domain of an ultraspiracle receptor where the exposure is disclosed in the specification to embrace exposing these cell at least the dimerization domain of an ultraspiracle receptor per se and also a DNA that encodes at least the dimerization domain of an ultraspiracle receptor (see page 19, for example).

The instant specification provides only scant and general guidance for the introduction of genes to a whole animal and provide no specific guidance. Nucleic acid based therapy is an unpredictable art and one of skill in the art is in need of specific guidance for any specific gene therapy. The art has shown that there are no routine methods and has further shown that one cannot expect positive results using methods known after the time of invention let alone what was known at the time of the instant invention. Ronald Crystal states [Science Vol. 270:404-410, 1995] at page 409 "[a]ll of the human transfer studies have been plagued by inconsistent results, the bases of which are unknown." Crystal reviews the state of the art of gene therapy and discusses the obstacles that still remain to effect nucleic acid based therapies and discusses the potential of nucleic acid based therapies. Verma et al [Nature Vol. 389:239-242, 1997]

discusses the problems of gene therapy artisan face even today. It is stated "[a]lthough more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story." and further "[t]he choice of tissue in which to express the therapeutic protein will ultimately depend on considerations such as the efficiency of gene delivery, protein modifications, immunological status, accessibility and economics." and also"[t]he Achilles heel of gene therapy is gene delivery, and this is the aspect . . ." It is clear, that although gene therapy provides promise for the treatment of disease and applicants invention to would be promising in a gene therapy, there are general obstacles faced by the artisan in the practice of gene therapy where the instant specification fails to provide adequate guidance to overcome these obstacles to practice the instant invention. This position is further taken in view of the disclosure of Orkin et al where it is also discussed the many problems of gene therapy that need to be overcome (see numbered pages 1, 3-14 and 30-35). It is clear from the art that the art of gene therapy is unpredictable and the state of the art at the time of invention would require specific guidance for any particular gene therapy where no routine methods are known. One of skill in the art would need to overcome the basic problems addressed in the art to practice the instant invention as it relates to gene therapy.

(11) Response to Argument

Appellant argues that the examiner has taken to narrow a view of the claimed invention. It is unclear how the interpretation is to narrow. The claims are drawn to nucleic acid manipulation in a subject. Appellant asserts that the claims do not require a nucleic acid based therapy since the term "nucleic acid therapy" is not recited in the claims. It is noted, however, that claims 18, 19, 39, 40, 41, 46, and 47 are specifically drawn to methods that include the modulation of expression of a therapeutic gene or genes that will impart a benefit to the subject of the invention, for example. It is further noted that the instant specification (at page 16, lines 27-30) defines "exogenous gene" to refer "to both wild type genes and therapeutic genes, which are introduced into the subject in the form of DNA or RNA, either natural or synthetic." With this definition it is clear that each and every claim is either specifically drawn to or specifically encompasses a nucleic acid based therapy since the instant claims require the introduction of foreign nucleic acids that encode therapeutic or beneficial genes to a subject. A further demonstration that the claimed invention clearly reads on and is directed to gene therapy is the fact that even "wild type" genes are defined (at page 17, lines 16-20, for example) to "include genes which encode a gene product: the substantial absence of which leads to the occurrence of a non-normal state in said subject; . . ." , and, even further, the specification defines (at page 17, lines 25-27, for example) a "therapeutic gene" to refer "to gene which impart a beneficial function to the host cell in which the gene is expressed." At pages 17-18 the language present in

claims 19, 41 and 48, for example, is used within the definition of "therapeutic genes" and such limitations are demonstrated at this cite to clearly and specifically embrace genes that express gene products that impart disease resistance (see page 18, line 5, for example). The definitions provided in the specification provide that it is clearly reasonable and even necessary to interpret the claims as specifically embracing nucleic acid based therapy. The first paragraph of the rejection of record indicates that subject matter which is enabled and the body of the rejection discusses that scope of the claimed invention that is not enabled. The utility for modulating nucleic acids in a subject clearly embraces gene therapy and the instant claims are clearly directed to such methods since the methods are clearly directed to the introduction and modulation of therapeutic genes in a subject. It is unclear, and Appellant does not provide what other reasons why one in the art might introduce and/or modulate the expression of therapeutic genes in a subject other than for therapy. Appellant argues that a considerable amount of experimentation is permitted, provided that it is merely routine, or provided that the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is the position of the examiner that at the time of invention (effectively 3/22/1990) reasonable guidance and direction are simply not present especially in view of the problems one in the art must overcome in order to practice the instant invention as evidenced by the references cited in the rejection of record. Appellant does not point to any guidance or direction in the specification. Appellant asserts further that in order to satisfy the enablement requirement, the specification need only disclose one method for making and using the

claimed invention that bears a reasonable correlation to the entire scope of the claim. It is noted that Appellant does not point to such a method that correlates to the entire scope nor provide any arguments why such a method would be correlative.

Appellant asserts that the instant claims require only that a subject contain a DNA construct encoding an exogenous gene under the control of a hormone response element; a receptor. . . [s]uch a method could be performed by, for example, inserting each of these elements into cells *in vitro*, e.g., in culture and then introducing those cells into a subject for various purposes including therapeutic purposes." Appellant then points to the specification at page 19, lines 29-35 and page 21, lines 23-28, which is the total extent of the guidance the specification provides for such *ex vivo* methodologies. It is noted that the claims are not limited at any point to *ex vivo* methodologies to the exclusion of an "exogenous gene" which has been defined to refer "to both wild type genes and therapeutic genes, which are introduced into the subject in the form of DNA or RNA, either natural or synthetic." The specification provides no specific guidance for *ex vivo* methodologies. Appellant points to Table 2 of Crystal et al for support of enablement of *ex vivo* methodologies. The information provided in Table 2 of Crystal et al was taken from several references of which all appear to be published after applicants effective filing date of 3/22/1990 and therefore can not be relied upon to evidence enablement for the claimed invention at the time of filing.

Appellant asserts that the examiners interpretation of the instant invention is improper and overly narrow interpretation of the invention. It has been clearly demonstrated by the examiner that the claims do in fact have a textual reference in the

actual language of the claims for how they have been interpreted and furthermore no limitations not clearly intended and specifically required by the definitions provided in the instant specification have been imported for the interpretation of the instant claims. It appears to the examiner that the interpretation of the claims by the examiner are clearly necessitated by the definitions in the specification and the nature of the invention itself which is clearly drawn to the manipulation of genetic material in a subject such that a beneficial/ therapeutic gene product is expressed. Appellant fails to provide a clear alternative to the examiners interpretation of the claimed invention with any clear explanation of why such interpretation, in view of the definitions in the specification would not clearly embrace and specifically read on nucleic acid based therapies.

Appellant assert that with the examiners profession of "ignorance" both the teachings of the specification and the high level of skill in the art are misplaced. Appellant points to paper No. 9, page 6 for support of the examiners professed "ignorance". Appellant then asserts "[I]t is axiomatic that enablement must be judged from the point of view of the skilled artisan, and not from the point of view of one apparently unfamiliar with the knowledge generally available in the art." It is noted that the questions raised by the examiner in paper No. 9, page 6, which have been asserted by appellant to be answerable by knowledge generally available in the art have not been answered by pointing to guidance in the specification, the prior art, or declaration, for example. Appellant relies though, on post filing art (Crystal et al), which cannot be used as evidence of enablement for the instant invention.

Appellant asserts that the examiners contention that "Applicant has not demonstrated that such [nucleic acid] constructs [for use in practicing the claimed invention] were available at the time of the invention." It should be noted that within the context of paper No. 12 the term "construct" was and is intended to refer to the "subject" of the claims and so that statement is not at odds with what subject matter has been indicated as enabled.

Appellant asserts that it is irrelevant to the instant claims whether gene therapy was an unpredictable art at the time of invention since the instant invention is not drawn to any specific gene therapy, but rather a method of modulating expression of exogenous genes. It is noted that the claims are not drawn to a specific therapy but are so broad as to include the modulation of any "therapeutic" or "exogenous" gene such that benefits are achieved, for example. In order to practice the full scope of the invention as appellant has claimed one in the art **must** manipulate the genetic material of a subject and thus the claims clearly depend on the state of the art of nucleic acid therapies, which state, at the time of invention, was unpredictable.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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May 9, 2002

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